IN THE COURT OF ARBITRATION FOR SPORT

FLOYD LANDIS	)	
	)	
Appellant,	)	
	)	
V.	)	**CAS 2007/A/1394**
	)	
UNITED STATES ANTI-DOPING AGENCY	)	
	)	
Respondent.	)	
	)	

WITNESS STATEMENT OF RICHARD V. CLARK

My name is Richard V. Clark. My address is 5 Moore Drive, Bldg 5.5606, Research Triangle Park, NC 27709.

Testosterone Metabolism – R V Clark **March 2008**

Background – Richard V. Clark, MD, PhD

Training: Bachelor's Degree, Biology – Occidental College, Los Angeles, CA, 1967; Master's Degree, Zoology – Duke University, Durham, NC, 1970; MD and PhD, Cell Biology (Biological Structure) – University of Washington, Seattle WA, 1977
Medical Training: Internship and Residency, Internal Medicine – University of Washington, Seattle WA, 1977-1980; Fellowship in Endocrinology and Metabolism – National Institutes of Health, Bethesda, MD, 1980-1984
Board Certification – Internal Medicine, 1981; Subspecialty Board Certification - Endocrinology and Metabolism, 1985; Medical Licensure: Washington – 1978 (inactive), Maryland 1983 (inactive), Georgia 1983 (active), North Carolina 1997 (active)
Academic Positions: Emory University School of Medicine – Assistant Professor of Medicine 1984-1990, Associate Professor of Medicine 1990-1992, both Division of Endocrinology and Metabolism; Duke University School of Medicine – Associate Professor of Medicine 1992-1997, Division of Endocrinology and Metabolism, Assistant Professor of Obstetrics and Gynecology 1996-1997, Division of Reproductive Endocrinology; Consulting Associate Professor of Medicine and Consulting Assistant Professor Obstetrics and Gynecology, 1997 to present

Pharmaceutical positions: GlaxoWelcome R&D-Principal Clinical Research Physician, Metabolic Clinical Pharmacology, 1997-2001; GlaxoSmithKline R&D - Head Metabolic Therapeutic Area, Clinical Pharmacology, 2001-2002, Senior Director, Metabolic Clinical Pharmacology, 2002-2006, Group Director, Metabolic Clinical Pharmacology, 2006-present
Scientific Societies: American College of Physicians – 1982 to present, Fellow 1989; American Society of Andrology – 1984 to present, Vice-President/President 1997-1999, Endocrine Society – 1986 to present;
Scientific Activities: 36 published manuscripts, 20 book chapter, and 63 presentations at national meetings of scientific societies; clinical research has focused on Endocrinology, Metabolism, and Andrology, the latter including studies on testosterone replacement with patches, sublingual tablets, gels, and oral formulations; Clinical Pharmacology at GSK, > 40 studies on pharmacokinetics of non-steroidal and steroidal compounds including 3 on oral testosterone.
Anti-Doping Activities: US Olympic Committee – T/E Advisory Panel – 2000; US Anti-Doping Agency – Anti-Doping Review Board - 2000 to present (including review of over 20 cases involving T/E ratios, and over 10 involving IRMS, Chief Medical Advisor for Mitchell Report on Use of Illegal Steroids and other Performance Enhancing Substances in Major League Baseball

It is my opinion that the difference of ≈ 6 delta/delta units between the 5 alpha diol metabolite and Pdiol endogenous reference compound in Mr. Landis's Stage 17 Sample establishes use of testosterone or its precursors. It is also my opinion that Mr. Landis's IRMS and T/E results for his eight Tour samples when taken together are consistent with what is known about steroid metabolism and the administration of exogenous testosterone or its precursors.

Testosterone Synthesis and Metabolism:

Allow me to start with a brief overview of testosterone synthesis and metabolism to provide some context to my discussion.

In men, testosterone is produced primarily in the testes by Leydig cells. In the Leydig cells, cholesterol is transported into mitochondria, the metabolic "engines" of the cell. There an enzyme array on the inner membrane of the mitochondria acts on cholesterol to make testosterone and other steroids as dihydrotestosterone (DHT). These enter the testicular vein to circulate to the rest of the body. The pituitary hormone, LH, stimulates testosterone production in the testes by both stimulating cholesterol uptake into the mitochondria and inducing the enzyme array to make testosterone. The levels of LH have a major role in determining the amount of testosterone produced. Another important source of androgens in the body is the adrenal gland which produces dehydroepiandrosterone (DHEA) and androstendione, plus some testosterone.

Testosterone in the body is primarily metabolized by enzymes in the liver and to a minor degree in other tissues as fat, skin, and muscle. These pathways have been discussed in detail by Dr Shackelton. In brief, the key initial step is the conversion of testosterone to

either 5α or 5β DHT, by either a 5α reductase enzyme or a 5β reductase enzyme. 5α or 5β DHT can then be converted to the 2 compounds of interest in IRMS studeis, 5α androstanediol (5 alpha diol) and 5β androstanediol (5beta diol). The stepwise conversion of testosterone to 5 alpha diol or 5 beta diol is partial source, but not the only source for these androstanediols. Two other metabolites, androsterone and etiocholanolone may also be used in IRMS studies, but many more steroids feed into these pools, especially the adrenal androgens. Therefore these are less sensitive markers of exogenous testosterone administration. Other steroids as progesterone do not enter the testosterone pathway at all, and can be used as endogenous reference compounds (ERC) in IRMS studies, as this case 5β pregnanediol (pdiol), the metabolite of progesterone.

These enzyme systems are complex, and the pathway preference to 5 beta diol or 5 alpha diol depends especially on the type, e.g. gel, oral or injection formulation, and to some extent the amount, of the compound being metabolized. In addition, there are significant differences between individuals in the relative activity of these 2 pathways.

Mr Landis' brief claims that the δ^{13}C-values for 5 alpha diol and 5 beta diol should be reasonably close, and not differ by more than 2.5 δ units, and therefore, greater differences are indicative of a flawed technique. This assertion is not supported from my substantial experience in steroid metabolism. Further, this assertion is not supported by data in the available, published literature which clearly show a high level of individual variability with differences as high as 4.3 δ units.

The studies of Shackelton (1997), Aguilera (1999, 2001), Maitre (2004), Baume (2006), and Schanzer (2007) show in detail the response of these metabolites, 5 beta diol and 5 alpha diol to applications of different formulations of testosterone: testosterone enanthate by intramuscular injection, testosterone undecanoate orally, and testosterone by cutaneous gel. A key feature of these studies is individual variability and the fact that 5 beta diol and 5 alpha diol do not necessarily track in tandem. While the difference in δ^{13}C-values for these is usually < 2.0, several individuals in these relatively small studies showed larger differences:

a) 2 of 5 men with max differences of 2.5 and 2.8 on testosterone enanthate intramuscularly (Shackleton, 1997),

b) 1 of 5 men with a max difference of 4.3 on testosterone intramuscularly (Aguilera, 1999),

c) 2 of 3 men with max differences of 2.8 and 3.1 on exogenous testosterone, probably testosterone enanthate intramuscularly (Aguilera, 2001),

d) one subject with max difference of ~ 3.0 on oral testosterone undecanoate (Maitre, 2004),

e) one subject (P9) with max differences of 3.3 and 3.0 on separate weeks on testosterone cutaneous gel (Schanzer, 2007), and

f) one additional subject (P3) from the Cologne Workshop presentation of the above study with a maximum difference of approx 2.3.

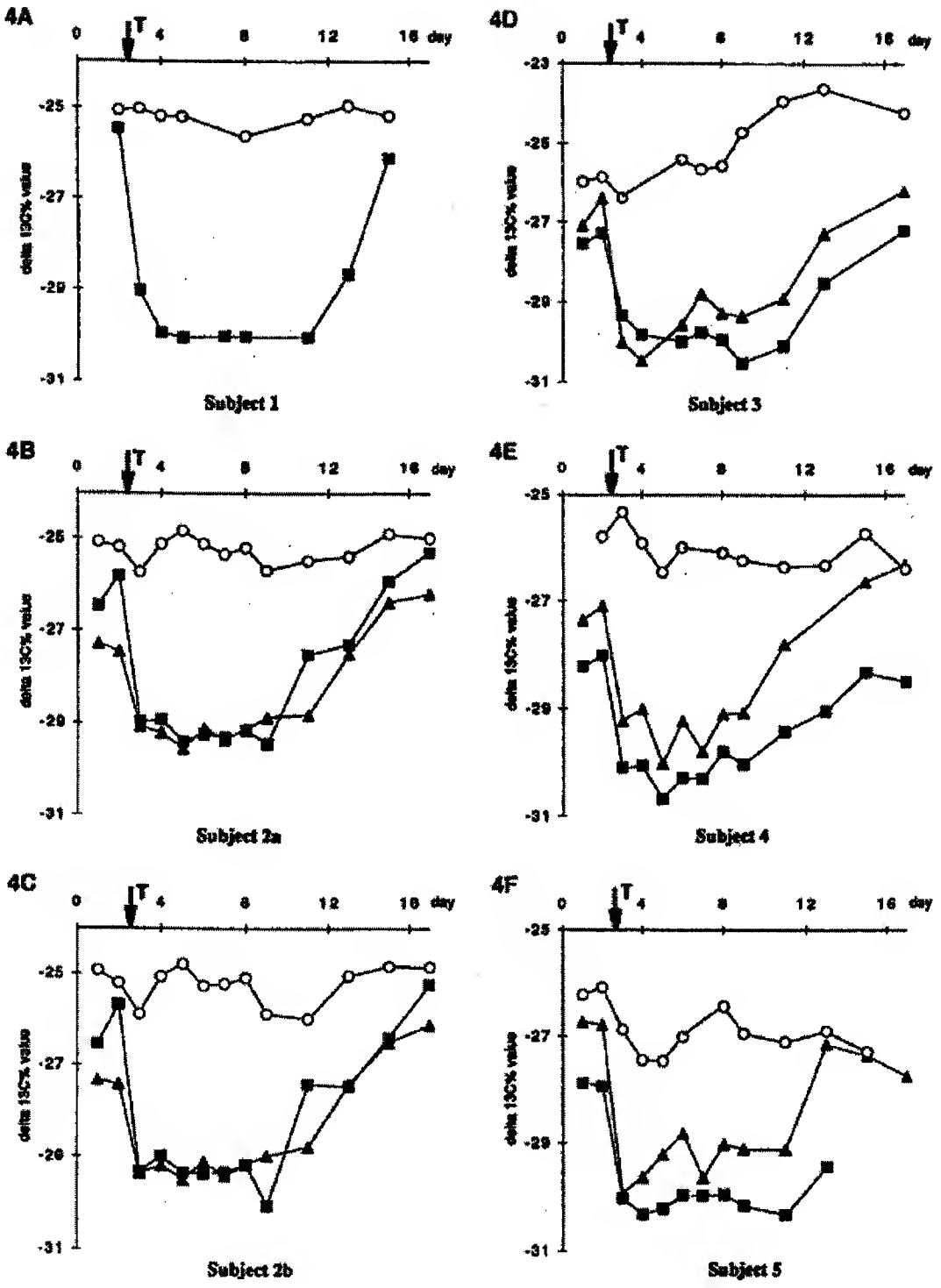
These studies clearly show significant variability between individuals in the enzymatic pathway preference in their bodies towards 5 alpha diol or 5 beta diol. This is evident in even these relatively small studies. Such individual variability in drug metabolism is very common. In my experience with pharmaceutical agents including testosterone, there can be a broad range of responses with drug levels on the same dose, commonly ranging 2-3 fold between high and low values, and in some instances as much as 5 fold or more. These are based on studies done in carefully controlled conditions and absence of other medications that can affect metabolism. A variety of factors contribute to this variability including differences in the rate and amount of absorption of the drug, genetic differences in enzyme activity and metabolism of the drug, and differences in the condition of the subject on a given day affecting how his/her body may respond. Subjects outside the controlled clinical research unit can show even greater variability, especially in the case of concurrent medications.

Further, these studies also showed that different testosterone formulations showed pathway preferences, so that cutaneous testosterone gel produced more 5 alpha diol (Schanzer, 2007), while oral and intramuscular testosterone produced more 5 beta diol (Maitre, 2004 and Shackleton, 1997, Aguilera, 1999). Also, these studies evaluated the wash-out period of these formulations and determined that single doses of intramuscular testosterone enanthate can induce demonstrable alteration of the δ^{13}C-values for 11 to 14 days after the injection (Shackleton, 1997), while oral TU can clear rapidly in 8 to 20 hrs in most individuals (Maitre, 2004). Similar data on T gel is not currently available, but studies on pharmacokinetics of blood testosterone indicate induction of stable levels during the first 24 hrs after single application and a 40-50% reduction from those levels at 48 hrs after single application (Wang, 2000, attached). While many factors not influencing serum testosterone can affect the levels of the urinary metabolites of testosterone, I would anticipate that the given the duration of blood levels, persistent changes in the δ^{13}C-values for 5 alpha diol and 5 beta diol could be evident for 48 hrs or longer, especially if a larger than standard replacement dose was used.

In addition, these studies clearly showed that T/E ratios do not correlate well with exogenous testosterone use, especially for oral and gel preparations where many subjects showed minimal changes in T/E, despite clear changes in 5 alpha and 5 beta diols.

There are many different combinations of oral testosterone, T gel, or DHT gel which could produce the ranges of metabolite δ^{13}C-values reported for Mr Landis' 8 Tour de France samples. In my opinion, these values are entirely consistent with manipulation with various testosterone and DHT products. For example, the values reported for stage 17 (20 July) are consistent with the use to T gel. Given the similar IRMS results, the elevated 5 alpha diol values on the last day of the Tour could be a carryover from doping before the previous day's race. Other than the T/E ratio of about 11 on Mr. Landis's Stage 17 sample, I would attach no significance to the small changes in the T/E ratios between his other seven samples.

Mr. Landis has questioned why a cyclist would take exogenous testosterone when the presumed benefit is on power strength rather than endurance. The available endurance studies have been done on healthy men under controlled circumstances that do not include extreme exertion activities. There are no available studies in men under these circumstances to understand what benefits testosterone may show. The riders in the Tour de France are under extreme exertion and stress, and likely have suppressed levels of testosterone. In these conditions, testosterone may have unappreciated benefits. Particularly, the use of testosterone in the later stages of the Tour as an anti-catabolic agent to counter the effects of stress induced elevation of cortisol which can accentuate muscle breakdown. While there are no direct studies on this, riders in the Tour de France and other cycling races must anticipate some benefit because they have continued to elect to dope with testosterone.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−30.42	−31.95	−25.87	4.8	6.3	1.19	1.25
−31.10	−31.76	−24.57	6.5	7.2	1.27	1.29
−31.43	−34.57	−28.14	5.2	6.4	1.20	1.32
−28.58	−31.04	−24.05	4.5	7.0	1.19	1.29
−28.85	−30.75	−22.97	5.7	7.8	1.25	1.34
−28.79	−31.25	−23.05	5.7	8.2	1.25	1.36
−29.64	−31.10	−22.60	6.0	8.5	1.27	1.38
−29.54	−32.30	−22.30	7.2	10.0	1.32	1.45
−29.84	−31.38	−21.87	8.2	9.7	1.38	1.45

I declare under penalty of perjury of the laws of California and New York that the foregoing is true and accurate. This statement was signed on March 7, 2008, in Research Triangle Park, North Carolina.

Richard V. Clark

Richard V. Clark

February 2008

Curriculum Vitae: Richard V. Clark, M.D., Ph.D.

Current Position:

Group Director, Metabolic Therapeutic Area, Metabolic CEDD
Clinical Pharmacology – Discovery Medicine
GlaxoSmithKline Research and Development, Research Triangle Park, NC

Mailing Address:

Clinical Pharmacology - Metabolic Diseases
GlaxoSmithKline, Bldg. 5.5606
PO Box 13398
Five Moore Drive
Research Triangle Park, NC 27709

Phone: (919) 483-5791
Cell: (919) 491-0671
Fax: (919) 315-4276
E-mail: richard.v.clark@gsk.com

Personal Data:

Married: Martha Carol Brimm, 1978, Seattle, Washington
Children: Elizabeth Anne Clark, 1983, Washington, D.C.
Home Address: 7 Surrey Lane, Durham, North Carolina 27707
Home Phone: (919) 493-1775

Degrees-Education:

B.A. 1967	Biology	Occidental College, Los Angeles, CA
M.A. 1970	Zoology	Duke University, Durham, NC
Ph.D. 1977	Cell Biology	University of Washington, Seattle, WA
M.D. 1977	Medicine	University of Washington, Seattle, WA

Postgraduate Training:

1977 - 1978: Internship, Internal Medicine, University of Washington, Seattle, Washington

1978 - 1980: Residency, Internal Medicine, University of Washington, Seattle, Washington

1979 - 1980: Chief Resident, Internal Medicine, Providence Medical Center, University of Washington, Seattle, Washington

1980 - 1983: Fellowship, Endocrinology and Metabolism, National Institutes of Health (DEB-NICHD), Bethesda, Maryland

1983 - 1984: Medical Staff Fellow, Director, Adult Endocrinology Ward, Developmental Endocrinology Branch, NICHD, NIH, Bethesda, Maryland

Professional Appointments:

1984 - 1990: Assistant Professor of Medicine, Division of Endocrinology and Metabolism, Department of Medicine, Emory University School of Medicine, Atlanta, Georgia

1990 - 1992: Associate Professor of Medicine, Division of Endocrinology and Metabolism, Department of Medicine, Emory University School of Medicine, Atlanta, Georgia

1987 - 1992: Director, Andrology Laboratory, Section of Internal Medicine, Emory Clinic, Atlanta, Georgia

1992 - 1997: Associate Professor of Medicine, Division of Endocrinology, Metabolism and Nutrition, Department of Medicine, Duke University Medical Center

1993 - 1996: Director, Clinical and Educational Programs, Division of Endocrinology, Metabolism and Nutrition, Department of Medicine, Duke University Medical Center

1996 - 1997: Assistant Professor, Division of Reproductive Endocrinology, Dept of Obstetrics and Gynecology, Duke University Medical Center

1997 - Present: Assistant Consulting Professor, Division of Reproductive Endocrinology, Dept of Obstetrics and Gynecology, Duke University Medical Center

1997 - Present: Associate Consulting Professor, Division of Endocrinology, Metabolism and Nutrition, Department of Medicine, Duke University Medical Center

1997 – 2001: Clinical & Medical Supervisor, Metabolic & Urogenital Diseases, (Principal Clinical Research Physician), Exploratory Development, US Clinical Pharmacology, Glaxo Wellcome Research and Development

2001 – 2002: Head, Metabolic Diseases Therapeutic Area, Clinical Pharmacology and Experimental Medicine, GlaxoSmithKline Research and Development

2002 – 2006: Senior Director, Metabolic Therapeutic Area, Clinical Pharmacology and Discovery Medicine, Metabolic CEDD, GlaxoSmithKline Research and Development

2006 – Present: Group Director, Metabolic Therapeutic Area, Clinical Pharmacology and Discovery Medicine, Metabolic CEDD, GlaxoSmithKline Research and Development

Board Certification and Honors:
Phi Beta Kappa, 1967
Bachelor's Degree, cum laude 1967
Predoctoral Traineeship (NIH-Univ. Wash.) 1971-1977
National Board of Medical Examiners, 1978
American Board of Internal Medicine, 1981
Subspecialty Boards - Endocrinology and Metabolism, 1985
Fellow - American College of Physicians, 1989

Professional Societies:

American Association for the Advancement of Science
American College of Physicians
American Diabetes Association
American Medical Association
American Society for Bone and Mineral Research
American Society of Andrology
American Urology Association
Endocrine Society

Medical Licensure:

Washington	1978, Inactive
Maryland	1983, Inactive
Georgia	1983
North Carolina	1992

Military Service:

U.S. Public Health Service - active duty, NICHD, National Institutes of Health, Bethesda, Maryland, 1980 - 1983

Administrative Responsibilities:

Clinical Coordinator, Adult Endocrinology Ward, NIH Clinical Center, NICHD, 1983-1984

Housestaff Selection Committee, Department of Medicine, Emory University, 1984-1986

Medical Records Committee, Emory University Hospital, 1984-1992

Medical Records Committee, Emory Clinic, 1989-1992

Drug Usage and Evaluation Committee, Emory University Hospital, 1991-1992

Director, Endocrinology Outreach Program, Department of Medicine, Duke University Medical Center, 1992-1993

Director, Fellow and Resident Training, Division of Endocrinology, Duke University Medical Center, 1992-1993

Chairman, Quality Improvement Committee, Division of Endocrinology, Duke University Medical Center, 1993-1997

Quality Improvement Committee, Department of Medicine, Duke University Medical Center, 1993-1997

Director, Clinical and Educational Programs, Division of Endocrinology, Duke University Medical Center 1993-1997

Executive Committee of the Clinical Practice Group (formly PDC Operating Committee), Department of Medicine, Duke University Medical Center, 1994-1997

Chairman, Task Force on Clinical Utilization of PA's and NP's in Medicine Subspecialty Clinics, Department of Medicine, Duke University Medical Center, 1996

Co-Chair, International Project Review Group, Clinical Pharmacology, Glaxo Wellcome Research and Development, 1998

Women in Clinical Trials Advisory Committee, Glaxo Wellcome Research and Development, 1998 – 2000, Chair, 2000 – 2003

Therapeutic Strategy Team – Urogenital Diseases, Glaxo Wellcome Reseach and Development, 1998 – 2000

Medical Project Group Leader - Compound GI181771, Galxo Wellcome Research and Development, 1999 - 2000

Exploratory Discovery Committee – Metabolic and Urogenital Diseases, Glaxo Wellcome Research and Develoment, 1999 – 2000

Metabolic-Musculoskeletal Therapeutic Area Strategy Team – GlaxoSmithKline Research and Development, 2000 - 2001

Metabolic Therapeutic Area, Technical In-Licensing Team – GlaxoSmithKline Research and Development, 2002 – present

Cardiovascular and Metabolic Medicines Development Matrix (Clinical Development Strategy Group) - GlaxoSmithKline Research and Development, 2004 – 2005

Chair, Policy Harmonization Committee for Women In Clinical Trials, GlaxoSmithKline Research and Development, 2004 – 2006

Director, Musculoskeletal Workstream, Metabolic CEDD GSK R & D, 2005 - present

Major Teaching Responsibilities:

Co-Director, Pathophysiology Course in Endocrinology and Metabolism for sophomore medical students, Emory University School of Medicine, 1985

Director, Section on Endocrinology and Metabolism, MKSAP VII Review Course, American College of Physicians, Atlanta, Georgia, May 5-6, 1986

Director, Section on Endocrinology and Metabolism, MKSAP VIII Review Course, American College of Physicians, Atlanta, Georgia, September 7-8, 1989

Director, Section on Endocrinology and Metabolism, MKSAP IX Review Course, American College of Physicians, Atlanta, Georgia, February 13-14, 1992

Director, "Update in Endocrinology Symposium," Duke University Medical Center, April 24, 1993

Director, "Harry T. McPherson Symposium in Endocrinology," Duke University Medical Center, November 4, 1993

Director, "Fall Endocrine Symposium," Duke University Medical Center, October 29, 1994.

Director "Current Issues in Osteoporosis," Duke University Medical Center, December 9,1995.

Funded Studies:

"Use of Sorbinil in treatment of diabetic retinopathy." Co- Investigator with Travis Meredith, M.D., Principal Investigator, Section of Ophthalmology, Emory Clinic, $124,00 Pfizer Pharmaceuticals, 1985-1988.

"Identification of serum risk factors for postmenopausal osteo-porosis as correlated with bone density." Co-Principal Investigator with Karen K. Steinberg, Ph.D., Nutritional Biochemistry Branch, Centers for Disease Control, $200,000, 1986-1992. "Androgen glucuronides as markers of androgen action." RO1, NIH-NIDDK, Co-Principal Investigator with Delwood C. Collins, Ph.D., Medical Research Service, VA Medical Center,

Atlanta, $507,000 (direct) 1989-1992. (Transferred with Dr. Collins to VMAC-University of Kentucky, Lexington, Kentucky, June, 1991.)

"Alprostadil Studies: fixed dose and long-term safety of alprostadil sterile powder (PGE1) formulation for use in patients with erectile dysfunction." Principal Investigator at site, Duke University Medical Center, $83,000, The Upjohn Company, 1992-1996.

"Topical Minoxidil in the treatment of organic impotence in patients with diabetes mellitus," Principal Investigator at site, Duke University Medical Center, $67,000, The Upjohn Company, 1993-1994.

"A Phase II, multicenter, double-blind, randomized research study of the safety and efficacy of Nutropin (Somatropin for injection) to improve physical and psychosocial well-being in growth hormone deficient adults." Principal Investigator at site, Duke University Medical Center, $105,000 Genentech, Inc., 1993-1995.

"A multicenter phase III study of the Safety and Efficacy of sublingual testosterone for hormone replacement therapy in hypogonadal men." Principal Investigator at site, Duke University Medical Center $69,000, Bio Technology General, 1994-1995.

"A Phase III, multicenter, double-blind, placebo controlled study to evaluate the efficacy and safety of recombinant FSH to improve the Fertility of men with oligospermia prior to in vitro fertilization." Principal Investigator at site, Duke University Medical Center $149,000, Serono Laboratories, 1993-1995.

"A Phase III, multicenter, non-comparative study to assess the safety and efficacy of Recombinant human Follicle-Stimulating Hormone (Gonal-F) in combination with human Chorionic Gonadotropin in

inducing spermatogenesis in men with hypogonadotropic hypogonadism." Principal Investigator at site, Duke University Medical Center, $37,000,
Serono Laboratories, 1995-1997.

"Bioavailability of a new transdermal therapeutic system of testosterone with an alternate backing material relative to Testoderm." Principal Investigator at site, Duke University Medical Center, $58,000, Alza Corp., 1996.

"Intercavernosal caverject sterile powder (alprostadil) in hypertensive patients with erectile dysfunction." Principal Investigator at site, Duke University Medical Center, $40,000, The Upjohn Company, 1996-1997.

"Phase II/III Evaluation of safety and efficacy of testosterone-gel for hormonal replacement in hypogonadal men." Co-principal Investigator at site, Duke University Medical Center, $150,000, Unimed Pharmacentical, 1997-1998.

"Phase II/III Evaluation of safety and efficacay of dihydrotestosterone-gel for hormonal replacement in elderly hypogonadal men." Co-principal Investigator at site, Duke University Medical Center, $100,000, Unimed Pharmacenticals, 1997-1998.

Scientific Review Activities:

Ad Hoc Review Committee, National Institute on Aging, RFA AG-91-12, "Use of Trophic Factors to Prevent Frailty," March 16-17, 1992.

Ad Hoc Reviewer, Scientific Journals:

- American Journal of Medicine
- Biology of Reproduction
- Clinical Pharmacology and Therapeutics
- Endocrinology
- Fertility and Sterility
- Journal of Andrology
- Journal Clinical Endocrinology and Metabolism
- International Journal of Andrology

United States Olympic Committee – Anti-Doping Advisory Panel, 2000

United States Anti-Doping Agency – Advisory Panel, 2000 - present

Scientific Society Activities:

Director, Post-Graduate Course, Annual Meeting, American Society of Andrology, April 21, 1990.
Local Arrangements Committee, Endocrine Society, Annual Meeting, 1990.

Chairman, Educational Policy and Postgraduate Course Committee, American Society of Andrology, 1989-1990.

Andrology Laboratory Certification Committee, American Society of Andrology, 1991-1993.

Awards Committee, American Society of Andrology, 1991-1992.

Chairman, Awards Committee, American Society of Andrology, 1992-1994.

Executive Council, American Society of Andrology, 1995-2000.

Vice President (President-Elect), American Society of Andrology, 1997-1998.

President, American Society of Andrology, 1998-1999.

Community Activities:

Scientific Committee, Georgia Chapter
National Osteoporosis Foundation, 1987, 1989-1990.

Vestry, Saint Bartholomew's Episcopal Church,
Atlanta, Georgia 1988-1991.

Board of Directors, Jerusalem House-Hospice
Atlanta Interdenominational Church Alliance, 1988-1989.

Board of Directors, Nicholas House (Homeless Shelter)
Chairman, Health Affairs Committee Nicholas House
Atlanta Episcopal Diocese, 1989-1992.

Parrish Council, Saint Stephen's Episcopal Church
Durham, North Carolina, 1995-1997

Co Chairperson, Earth Stewardship Committee
Saint Stephen's Episcopal Church
Durham, North Carolina, 1995-1997, 1999-2001

Vestry, Saint Stephen's Episcopal Church
Durham, North Carolina, 2000 – 2003

NC Diocesan Representative, Saint Stephen's Episcopal Church
Durham, North Carolina, 2001 - 2003

Rector Search Committee, Saint Stephen's Episcopal Church
Durham, North Carolina, 2004

Publications:

R.V. Clark, "Behavioral thermoregulation by the white rat at high ambient temperatures, J. Exp. Zool. 178: 387-392, 1971.

R.V. Clark, "Three-dimensional organization of the testicular interstitial tissue and lymphatic space in the rat," Anat. Rec. 184: 203-226, 1976.

R.V. Clark, "Ultrastructural studies on the rat testis: organization of the interstitial tissue and effect of heat on the seminiferous epithelium," Doctoral thesis, Department of Biological Structure, University of Washington, Seattle, 1977.

V.L. Pascucci, R.L. Yeager, R.J. Sherins, R.V. Clark, J.F. Gallelli, and D.C. Chatterji, "Quantitation of testolactone 4,5-dihydrotestolactone in plasma and urine using high performance liquid chromatography," J. Chromatography 277: 79-85, 1983.

B.D. Albertson, W.C. Hobson, B.S. Burnett, P.T. Turner, R.V. Clark,R.J. Schiebinger, D.L. Loriaux, and G.B. Cutler, "Dissociation of cortisol and adrenal androgen secretion in the hypophysectomized, ACTH-replaced chimpanzee," J. Clin. Endocrinol. Metab. 59:13-18, 1984.

C. Eil, G.T. Gamblin, J.W. Hodge, R.V. Clark, and R.J. Sherins, "Whole cell and nuclear androgen uptake in skin fibroblasts from infertile men," J. Andrology 6:365-371, 1985.

N.B. Watts, and R.V. Clark, "Endocrinological testing in patients with pituitary tumors," Contemp. Neurosurg. 7:1-6, 1985.

R.V. Clark, and R.J. Sherins, "Use of semen analysis in the evaluation of the infertile couple," in Male Sexual Dysfunction: Diagnosis and Management of Hypogonadism, Infertility, and Impotence, R.F. Santen and R.S. Swerdloff (eds), Marcel Dekker, Inc., pp. 253-266, 1986.

J.D. Booth, G.R. Merriam, R.V. Clark, D.L. Loriaux, and R.J. Sherins, "Evidence for Leydig cell dysfunction in infertile men with a selective increase in plasma FSH," J. Clin. Endocrinol.Metab. 64: 1194-1198, 1987.

N.B. Watts, S.S.P. Gebhart, R.V. Clark, and L.S. Phillips, "Postoperative management of diabetes mellitus: "steady state" glucose control with a bedside algorithm for insulin adjustment." Diabetes Care: 10:722-728, 1987.

R.V. Clark, and G.T. Tindall, "Hyperprolactinemia and galactorrhea," in Medicine for the Practicing Physician, 2nd edition, J.W. Hurst (ed), Butterworth Publ., pp. 508-510, 1988.

R.V. Clark, "Male hypogonadism," in Medicine for the Practicing Physician, 2nd edition, J.W. Hurst (ed), Butterworth Publ., pp. 514-516, 1988.

R.V. Clark, "Male infertility," in Medicine for the Practicing Physician, 2nd edition, J.W. Hurst (ed), Butterworth Publ., pp. 516-518, 1988.

R.V. Clark, "Management of the surgical patient with pituitary insufficiency," in Medical Management of the Surgical Patient, 2nd edition, M.L. Lubin, K. Walker, and R. Smith (eds), Butterworth Publ., pp 316-318, 1988.

A.S. Burris, R.V. Clark, D.J. Vantman, & R.J. Sherins, "A low sperm concentration does not preclude fertility in men with isolated hypogonadotropic hypogonadism following gonadotropin therapy," Fertil. Steril. 50:343-347, 1988.

H.R. Nankin, T. Lin, and R.V. Clark, "Disorders of male reproductive function," in Diagnostic Endocrinology, W.T. Moore and R. Eastman (eds), B.C. Decker, Inc., pp. 247-281, 1989.

R.V. Clark, and R.J. Sherins, "Treatment of men with idiopathic oligospermic infertility using the aromatase inhibitor, testolactone: results of a double blinded, randomized, placebo controlled trial with crossover," J. Andrology, 10:240-247, 1989.

B.F. Walker, C.J. Gunthel, J.A. Bryan, N.B. Watts, R.V. Clark, "Disseminated cryptococcoses in an apparently normal host presenting as primary adrenal insufficiency: diagnosis by fine needle aspiration," Am. J. Med. 86:715-717, 1989.

S.S.P. Gebhart, N.B. Watts, R.V. Clark, G. Umpierrez, D. Sgoutas, "Reversible hypogonadotropism as a measure of critical illness in postmenopausal women," Arch. Intern. Med. 149: 1637-1641, 1989.

K.K. Steinberg, L.W. Freni-Titulaer, G. Depuey, D.T. Miller, D. Sgoutas, C. Corrali, D. Phillips, T.N. Rogers, R.V. Clark, "Sex steroids and bone density in premenopausal and premenopausal women," J. Clin. Endocrinol. Metab., 69:533-539, 1989.

R.V. Clark, and R.J. Sherins, "Male Infertility," in Principles and Practice of Endocrinology and Metabolism, K.L. Becker (ed), Lippincott, pp. 985-991, 1990.

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